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TITLE: A Phase II Trial on the Effect of Low-Dose versus High-Dose Vitamin D Supplementation on Bone Mass in Adults with Neurofibromatosis 1 (NF1)

PRINCIPAL INVESTIGATOR: David Viskochil, MD, PhD

CONTRACTING ORGANIZATION: University of Utah
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13. SUPPLEMENTARY NOTES

14. ABSTRACT
This study has not been fully implemented. Clinical trial regulatory processes have taken more time than anticipated in the Statement of Work. An IND from the FDA to use high-dose vitamin D in the NF1 (neurofibromatosis type 1) population has been obtained, as requested by the University of Utah IRB. The study was approved both by the University of Utah IRB and the DoD USAMRMC ORP HRPO. Ethics board approval from UBC has been approved by HRPO, and U of Cincinnati is under review. The University of Hamburg is working with the European Union Clinical Trials group (EurodratCT) to implement this study, and a document of agreement to perform a joint clinical trial with the University of Utah has been executed. The Clinical Trials office in Hamburg has reviewed the proposal and we have accommodated the custodianship of study drug, cholecalciferol, from the manufacturer in Canada directly to Germany. Reviews from the IRBs and EurodratCT have led to revision of the manual of operations, which is included in this report. We have instituted monthly conference calls, which has enabled us to finalize the manual of operations to accommodate all 4 sites.

15. SUBJECT TERMS
NF1, vitamin D, osteopenia, adults, double-blind randomized trial

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1. INTRODUCTION:

Neurofibromatosis type 1 (NF1) is a multisystem disease, and many patients have skeletal manifestations that fall into three general categories: (1) characteristic focal lesions, (2) short stature, and (3) osteomalacia, osteoporosis, or low BMD (bone mineral density), which occurs in almost all affected individuals by age 50. Vitamin D therapy appears to have some benefit in treating osteoporosis in the general population, and administration of vitamin D in a dose that maintains the serum 25-hydroxy vitamin D level above 30 ng/mL significantly improves BMD in individuals with NF1. These observations led to the development of a phase II clinical trial to evaluate the effectiveness of vitamin D_3 dosing in NF1 patients. This study is designed to assess the efficacy of oral vitamin D_3 and calcium therapy to prevent abnormal loss of bone mass in adults with NF1. The clinical trial is a double-blind, dose comparison of efficacy of high-dose versus low-dose vitamin D_3 on preservation of bone density as measured by DXA scanning after 2 years of treatment. It compares 2 groups of adults with NF1 between 25 and 40 years of age with insufficient levels of serum 25-hydroxy vitamin D at study entry. Participants are randomized and one group will take 600 IU and the other will take 4,000 IU on a daily basis for 2 years. Participants and investigative teams are blinded to the vitamin D_3 dose. The primary outcome measure is bone mineral density at the spine and hip. Secondary patient reported outcome (PRO) measures include a quality of life questionnaire (SF-36), fracture history survey, and activity survey.

2. KEYWORDS:

25(OH)D = 25-hydroxy vitamin D
BMD = bone mineral density
CCTS = Center for Clinical & Translational Science at the University of Utah
Cholecalciferol=vitamin D3
CIN = University of Cincinnati enrollment center
CGRP = Clinical Genetics Research Program
DEXA = dual energy x-ray absorptiometry
Ddrops = formulation of cholecalciferol (vitamin D_3)
DXA = dual energy x-ray absorptiometry
FDA= Federal Drug Administration
HAM = University of Hamburg enrollment center
IRB = Institutional Review Board
NF1 = neurofibromatosis type 1
PCTO = Pediatric Clinical Trials Office at the University of Utah
PRO= Patient Reported Outcome
UBC = University of British Columbia enrollment center

3. OVERALL PROJECT SUMMARY (STATEMENT OF WORK)

Overall Objective: Determine best dose of cholecalciferol supplementation to optimize maintenance of bone mineral density in adults with neurofibromatosis type 1 (Funding: 9/30/2012 -09/29/2016; 48 months)

I. Major Goal - Assemble a cohesive multi-center team for phase II clinical trial

Task I.1 (mo 0-2): compile subcontracts between UTA and the following sites UBC (University of British Columbia, Canada), CIN (University of Cincinnati, USA), HAM (University of Hamburg, Germany).

Subcontracts have been distributed by the University of Utah Office of Sponsored Projects. The University of Cincinnati has submitted invoices, and payout for October 1, 2014-September 30, 2015 was $58,000. It has requested carryover from year 2 to year 3, cognizant of the need hold funds for an extension of the study since it has been over 2 years in getting underway. The University of British Columbia has submitted invoices, and payout for October 1, 2014-September 30, 2015 was $26,877. The subcontract with University of Hamburg has been executed, but no invoices have been sent for payment. The University of Utah has charged $47,412 over the period of October 1, 2014-September 30, 2015.

The European Union Clinical Trials group (EurodratCT) has approved the study contingent on assurance that drug is shipped directly from the manufacturer to the University of Hamburg research pharmacy. No funds have been allocated to HAM.

Task I.2 (mo 2): conduct an organizational face-to-face meeting between 4 PIs and data monitor

This meeting is contingent on changes to protocol after IRB approval from all institutions, and it will be scheduled after approval from DoD USAMRMC ORP HRPO for all 4 sites. Two of 4 sites have DoD USAMRMC ORP HRPO approval. U of Cincinnati is under review, and U of Hamburg will submit to ethics board after the manual of operations is translated to German and once approved in Hamburg will be retranslated to English and sent to U of Utah and DoD USAMRMC ORP HRPO for review. Agreement on implementation of the study at multiple sites may allow us to begin recruitment in March 2016 and this meeting can take place at the time of the NF Conference in Austin Texas in June, 2016.

Task I.3 (mo 2-3): assemble manual of operations and distribute to each site

A manual of operations has been amended as issues regarding protocols under review by IRBs at the respective institutions required modification. The manual is appended.

Task I.4 (mo 1-2): establish lines of communication between PIs, coordinators, financial managers at each site

As part of the subcontracts appropriate financial managers have been identified at each of the 4 institutions. Email has been the primary line of communication. Monthly conference calls have been initiated in summer of 2015.

Task I.5 (mo 2): establish long-term contract with courier for shipment of samples, supplies, study drug

A proposal with Markem, an international courier service was initially established, but is under review now that the University of Hamburg clinical trials office will accept direct shipment of vitamin D to the University of Hamburg whereby relabeling will take place according to randomization from the medical monitor at the U of Utah. UBC and CIN are determining the best approach for shipment with their respective research pharmacies. Negotiations on final pricing for shipping drug and serum samples has not been completed, pending changes that may be introduced by the IRB approval process at all 4 institutions.

Task I.6 (mo 7-48): maintain regular monthly reports regarding enrollment, data collection, and safety issues

Enrollment has not begun. It is anticipated for March 2016 for U of BC, U of Cincinnati, and U of Utah to correspond to the seasonal basis of serum 25-OH vitamin D. Enrollment at U of Hamburg will begin upon human subjects research approval from DoD USAMRMC ORP HRPO.

II. Major Goal - Enroll human subjects into a phase II clinical trial with vitamin D3 supplementation

Task II.1 (mo 0-5): establish IRB approvals at 4 sites and USAMRMC ORP HRPO review

Approval from the FDA to use the 4,000 IU dosing of cholecalciferol in the adult NF1 population was obtained in September of 2013. An annual report has been submitted to the FDA. The only significant change has been an alteration in the concentration of Ddrops. The manufacturer will provide a concentration of 300 IU/drop and a concentration of 2,000 IU per drop. Randomized participants will both take 2 drops per day instead of 1 drop per day.

IRB at the University of Utah approved the clinical trial application at the end of November, 2013. Minor amendments reflecting changes in the manual of operations and personnel changes have been submitted for continuing review, which was approved November 30, 2015.

USAMRMC ORP HRPO approved a modified U of Utah IRB-approved protocol in February, 2014, and the continuing review in November 2014.

UBC ethics committee approval was established, and USAMRMC ORP HRPO approval was provided October 20, 2015.

U of Cincinnati IRB protocol was approved by the local IRB and submitted to the USAMRMC ORP HRPO on May 5, 2015. Additional continuing review locally was obtained September 21, 2015.

U of Hamburg protocol is under revision as reflected in our updated manual of operations, and once translated to German will be submitted to its ethics committee. The CRFs have been translated into German and will be submitted for ethics review once the manual of operations is completed and final revision completed by the U of Utah medical monitor office.

Task II.2 (mo 1): confirm oversight by an external safety monitor

The safety monitor is Dr. Richard Kanner from the Center for Clinical and Translational Sciences (CCTS) at the University of Utah, and he will serve as chair of a 3-member committee to oversee safety issues related to the study. They will meet face to face or by teleconference every 6 months to review recruitment and participant enrollment, monitor summarized data collection from the 4 sites as submitted to the Pediatric Clinical Trials Office (director, TBD), review adverse events, and monitor serum collection and disposition of samples.

Task II.3 (mo 4-23): recruit adults with NF1 to consider participation in clinical trial

C*oordinators at each site have alerted their respective adult NF1 population of the upcoming trial. Enrollment will commence when all 4 sites have achieved institutional human subjects protection approval.*

Task II.4 (mo 3): establish failsafe mechanism to determine pregnancy status prior to densitometry

The manual of operations specifies local coordinator oversight of urine pregnancy testing prior to the initial DXA scan and exit DXA scan. Coordinators will review of reproductive history with females throughout the study.

Task II.5 (mo 6-15): first enrollment period for 25(OH)D serum screening/vitamin D3 supplementation

Pending IRB approval at each site and final approval of the DoD HSPO for each site. March 2016 is the target date for UTA, UBC, and CIN. Enrollment at HAM is dependent on IRB review.

Task II.6 (mo 18-23): second enrollment period for 25(OH)D serum screening/vitamin D3 supplementation

To commence in Spring of 2017.

Task II.7 (mo 6-15; mo 18-23): verify enrollment with unique identifier by hard copy and electronic means

Not applicable.

Task II.8 (mo 5-48): maintain ongoing IRB approval

Amendments will be introduced to each of the sites as a final DoD HSPO approval is established for all 4 sites. Approvals from the 3 subcontracted sites will be collated by the lead coordinator at the University of Utah. These will be forwarded to the DoD HSPO in a timely fashion.

Task II.9 (mo 12, 24, 36, 48): annual review by safety monitor and distributed to each IRB and USAMRMC

Per IRB stipulation, safety reviews of adverse events will take place every 6 months. Data including a spreadsheet of all adverse events will be compiled by the coordinator at the University of Utah and submitted to the safety monitoring committee for review. The FDA also will be appraised of adverse events, and a summary of the safety monitoring committee will be provided to the FDA as part of the annual report of cholecalciferol use in adults with NF1.

Task II.10 (mo 18-27; mo 30-35): data monitor safety assessment for loss of bone mineral density of >7% loss

Not applicable.

III. Major Goal - Obtain laboratory, bone density, and survey data on participants in the study

Task III.1 (mo 3-5): establish scheduling processes for each enrollment center

Scheduling processes have been established at the UTA site through CCTS facilities as an approved protocol. With IRB approval at UBC and CIN, scheduling processes have been established. HAM scheduling processes have not been approved as part of ethics review panel.

Task III.2 (mo 3-5): complete assessment of cross-calibration of DXA machines at 4 sites

DXA machines and scanning teams have been established at each of the 4 sites. Internal standardization of each machine is performed on a daily basis, and the need for a phantom for cross-calibration of each machine is under review. There is a possibility that the same DXA machine will not be in use from the initial DXA to the exit DXA scan 2 years later. Each site will cross-calibrate machines so that data collected on one machine can be adjusted as part of this process. Between site calibration may not be necessary.

Task III.3 (mo 2-5): assemble all data collection forms, blood collection kits, and CDs at each enrollment center

Clinical report forms (CRFs) with revisions have been included in IRB applications. HAM has translated the forms to German and will submit as part of ethics panel review. Blood collection kits have been identified. Electronic data collection processes are in

transition.

Task III.4 (mo 3-5): establish and verify access to the study-specific, web-based, password-protected database

This will be accomplished in the Medical Monitor's office. Data submission will be set up at each of the 4 sites and data will be reviewed by the medical monitor team.

Task III.5 (mo 4): develop mechanism to obtain blood samples for 25(OH) vitamin D screening (ARUP Lab)

Pending final approval of contract with the shipping agency.

Task III.6 (mo 6-15; mo 18-23): obtain serum 25(OH)D on 316 enrollees across 4 enrollment centers

N/A

Task III.7 (mo 5-7): document processes for timely notification of serum 25(OH)D results and randomization

N/A

Task III.8 (mo 6-15; mo 18-23): Randomize 226 participants to either 600 IU or 4,000 IU of daily vitamin D3

N/A

Task III.9 (mo 6-15; mo 18-27; mo 30-39; mo 42-47): perform initial DXA scans, brief physical exam, and perform surveys on 226 participants at 3 time-points

N/A

IV. Major Goal - Monitor data acquired throughout the study period

Task IV.1 (mo 3-5): establish confidential procedures for monthly data acquisition monitoring and reporting

The medical monitor in the pediatric clinical trials office at the University of Utah have active procedures with other trials. Now that IRB approvals are established at UBC and CIN with executed subcontracts, coordinators at each site will be trained in data submission by staff at the medical monitors office.

Task IV.2 (mo 3-5): establish access for the data monitoring team to the study-specific database

CRFs have been provided to the medical monitoring team. Personnel in the Pediatric Clinical Trials Office have not been mobilized, and a final decision on the database to be utilized will be made at a meeting with the acting director of the PCTO scheduled for December 7, 2015.

Task IV.3 (mo 6-48): verify quality of data acquisition with coordinators at each enrollment center

N/A

Task IV.4 (mo 18-21): perform interim analysis on a subset of enrollees at 1 year for change in BMD of hip

N/A

V. Major Goal - Provision of vitamin D3 and calcium supplementation

Task V.1 (mo 3-5): verify formulation of vitamin D3 in the form of Ddrops

Documentation has been provided by the manufacturer, Ddrops, on the formulation and distribution of batches of Ddrops to the University of Utah medical monitor team. The manufacturer has altered the concentrations of vitamin D3. Originally, it was to concoct concentrations of 600 IU per drop and 4,000 IU per drop. This has been modified to 300 IU per drop and 2,000 IU per drop. Thus, randomized participants will take 2 drops of either low-dose or high-dose vitamin D3.

Task V.2 (mo 5): distribute Ddrops from dispensing site in Ontario Canada to the University of Utah

This has not been initiated pending final negotiations between each site and their respective research pharmacy. HAM has been approved to receive the shipment directly from Ddrops, but UBC and CIN are still negotiating. The research pharmacist at UTA is prepared to receive shipment for all anticipated enrollees, and have approved the shelf life of Ddrops so that storage on site is feasible.

Task V.3 (mo 2-4): establish failsafe methodology to mask the bottle of Ddrops and provide unique identifier

The medical monitor office has established the plan to remove the Ddrops manufacturer label and replace with a label that enables the randomization team to allocate relabeled study drug upon receipt of notification of enrollment at each of the 4 sites. This entails having the designated vials (low-dose and high-dose) in storage at the respective site's research pharmacy only to be released to a randomized participant by the site clinical research coordinator. Affirmation that the unique identifier of the participant is linked to a unique identifier on the vial will be performed by the local site coordinator and the

data monitoring team, under the direction of the medical monitor.

Task V.4 (mo 6-15; 18-23): randomize participants with a unique bottle number/communicate to site coordinator

N/A

Task V.5 (mo 6-47): implement methods to educate/monitor participants on aspects of vit D3 and calcium intake

N/A

Task V.6 (mo 12-41): ensure resupply of Ddrops bottle corresponds to the initial bottle designation

N/A

Task V.7 (mo 6-48): monitor potential side effects of vit D3 supplementation

CRFs for adverse event reporting have been developed and included in the protocols submitted for IRB approval and the revised manual of operations.

VI. Major Goal - Establish a bio-repository of serum samples

Task VI.1 (mo 2-5): develop protocol to process samples at the CGRP freezer storage facility at the U of Utah

This protocol has been approved by the FDA and the U of Utah IRB. Retention of serum after completion of the study has been addressed in IRB protocols. These specimens will be destroyed, unless the participant has signed other IRB approved consent for retention of sample for other studies.

Task VI.2 (mo 6-47): ensure participant identifier corresponds to consent to store samples for future studies

N/A

Task VI.3 (mo 6-47): document acceptance of storage sample in the CGRP database and vit D3 study database

The process for storage of sample in the CGRP database has been established, but linkage of information for the vitD3 study database has not been established.

VII. Major Goal - Data analyses

Task VII.1 (mo 6-48): collect data on all enrollees both by hard copy forms and in the study-specific database

N/A – no enrollees as of yet.

Task VII.2 (mo 6-48): validate data collection on a monthly basis by data monitor

N/A

Task VII.3 (mo 7-48): verify accuracy of data collection by enrollment center coordinators

N/A

Task VII.4 (mo 47-48): perform comparison of low-dose vit D3 versus high-dose vit D3 on data collections

N/A

Subcontracts between U of Utah (UTA) and CIN, UBC, and HAM

Organization name: Cincinnati Children's Hospital Medical Center (CIN)
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Organization name: University of British Columbia (UBC)
Organization address:
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Investigators: Jan M. Friedman, MD, PhD Collaborators: David Kendler, MD

Organization name: University Medical Center Hamburg-Eppendorf (HAM)
Organization address:
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Department of Finance University Medical Center Hamburg-Eppendorf
Martinistrasse 52 20246 Hamburg, Germany
Investigators: Victor F. Mautner, MD Collaborators: Said Farschtshi, MD

4. KEY RESEARCH ACCOMPLISHMENTS – None to report

5. CONCLUSION: The implementation of this trial has been delayed for 3 main reasons. The initial assessment by the University of Utah IRB that supplementation of vitamin D required an FDA exemption led to an application that resulted in a denial of exemption, and requirement for an IND for the administration of high-dose (4,000 IU) of cholecalciferol to a selected population of NF1 patients. Approval of an IND through the FDA was obtained in September of 2013. We could then begin the IRB approval process at the University of Utah, which was completed in November of 2013 and reviewed and approved by the DoD HSPO in February of 2014. The next major hurdle has been regulatory compliance with the European Union Clinical Trials organization (EurodratCT) for implementation of a clinical trial through the University of Hamburg. We are working with EurodratCT to finalize our protocol, especially as it relates to the manufacture and transportation of study drug, cholecalciferol. The EurodratCT also required the establishment of a designated legal representative from the sponsoring agency, which was established as the University of Utah. We combined the designated legal representative language with the subcontract, which has been executed. We had anticipated working directly with the University of Hamburg, and the additional regulatory oversight by the EurodratCT was not foreseen in our original application. The administrative costs of this additional regulatory component are provided by the University of Hamburg. We are finalizing the manual of operations to reflect the combined needs of all 4 sites and the medical monitoring team. Of all 4 sites, HAM is anticipated to have the most adults with NF1 who are insufficient for 25(OH) vitamin D. Without its full participation, it would be nearly impossible to enroll a large enough sample size to achieve statistical significance. Therefore, as a consensus we elected to hold off on recruitment/enrollment until the University of Hamburg completed negotiations with the EurodratCT. We are now poised to complete the ethics review in Germany to begin recruitment in Spring of 2016, and it is anticipated that UBC, CIN, and UTA will be ready to enroll in March, 2016. It is recognized that delays in implementation of the trial will likely lead to cost overrun. Dr. Viskochil will seek no-cost extension approvals to enable funding to the subcontracted sites, and he anticipates seeking additional funding from outside sources, including the Childrens Tumor Foundation (CTF) as supplemental funding up to $150,000 as a CTF-sponsored Clinical Trial Award. The next RFA is for application is early summer of 2016.

There have been changes in personnel at the UTA site. Heather Hanson was our initial clinical research coordinator, and she was replaced by Carrie Bailey as lead coordinator. Ms. Bailey will work with the other 3 site coordinators and oversee Carlos Barbagelata who will enroll and perform data entry at the UTA site. In another significant change of personnel, Dr. Michael Dean has replaced Dr. Michael Spigarelli as the interim director of the Pediatric Clinical Trials Office (PCTO), which is the center that will serve as the medical monitor team for all aspects of this trial. A director position is posted, but in the interim we will be working with Dr. Dean to implement monitoring of enrollment, specimen data analyses, randomization, DXA collection, and other electronic data entry to follow progress of the trial and adverse event reporting. The electronic database harboring data entry from each of the 4 sites has been initially set up by Bernie LaSalle in the CCTS (Center for Clinical Translation Sciences), but with the change in personnel in the medical monitoring group a final decision will be made regarding use of the database

utilized by the medical monitoring team in the PCTO. A hybrid plan may be invoked for the ease of data entry (CCTS) and independent assessment of data documentation and patient monitoring (PCTO). A meeting to resolve this issue is set for December 7, 2015.

Manual of Operations

A Phase II Trial on the Effect of Low-Dose versus High-Dose Vitamin D Supplementation on Bone Mass in Adults with Neurofibromatosis Type 1 (NF1)

4 Nov 2015

University of Utah IRB_00055719
University of Utah IRB Approval 11/20/2013
University of Utah Amendment approval 2 /11/2014

Table of Contents

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Data Safety monitor: Richard Kanner, richard.kanner@hsc.utah.edu

Medical Monitor: TBD

Data Manager: Bernie LaSalle, Bernie.lasalle@hsc.utah.edu

Participating Sites

University of Utah (Salt Lake City, UT, USA)
Principal Investigator: David Viskochil MD, PhD
Coordinator: Carrie Bailey, BS, CCRC

University of British Columbia (Vancouver, CA)
Principal Investigator: J.M Friedman MD. PhD
Coordinator: Patricia Birch RN

University of Cincinnati (Cincinnati, OH, USA)
Principal Investigator: Elizabeth Schorry MD.
Coordinator: Sara Manning

University of Hamburg (Hamburg, Germany)
Principal Investigator: Victor Mautner MD.
Coordinator: Claudia Wargel

Site PI contact info:

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GENERAL INFORMATION

Each site has been sent copies of the study protocol, consent form and associated paperwork for IRB/Ethics submission.

We ask that you try to keep your IRB's /Ethics board submissions as close to the same layout /format and as possible (based on your site guidelines).

Once our site has approval, please send the approved documents back to Utah for further submission to both the Army and Utah's IRB for approvals.

Note: Sites cannot enroll for this study until both approvals have been received by Utah and your site has been notified by Carrie Bailey, BS, CCRC or Dr. Viskochil that you can begin enrolling.

Description of Recruitment Process:
Recruitment will be in compliance with local site IRB requirements and GCP/ICH guidelines.

Enrollment/Eligibility:
The target population - adults with neurofibromatosis type 1 (NF1) between the ages of 25 and 40 years who are insufficient for vitamin D, as defined by serum testing at time of enrollment and meet all inclusion/exclusion criteria as defined by the protocol.

Informed Consent Process:
The study coordinator at each site will be responsible for explaining the study, answering questions, and obtaining informed consent. The principal investigator at each site will also need to be available for answering questions. The study will be explained in advance of the screening visit and the consent form will be signed and witnessed prior to or at the time of the first screening visit. All potential study participants will be adults who are competent to understand the study and sign consent on their own behalf. Each subject will have at least one week to decide whether or not they wish to participate. Participants will have full access to the investigative team throughout the clinical trial.

Coordinators at each site will telephone participants every 3 months to review any issues or concerns with respect to the trial. The vitamin D_3 and calcium supplementation diary will be reviewed, and any potential side effects or adverse effects will be documented and discussed at that time.

Participant Support:
All subjects will be provided participant compensation equivalent to US$25 for enrollment and screening blood test for the determination of serum 25(OH)D. Subjects will be offered participant compensation equivalent to US$50 per clinical visit at the start of the study, at 12 months, and at 24 months. These visits include DXA scans on entry and exit, blood specimen on entry, 1 year, and exit at 2 years, physical activity survey, calcium intake questionnaire, a fracture history, a quality of life survey, and a brief clinical exam for each visit.

Record Keeping for Study Data
Data collected from this study will be maintained as electronic data entered into a database designed and maintained in the Center for Clinical & Translational Sciences at the University of Utah. This database has a tiered access with each of the four centers having password-protected access to data

entered from their respective site. These data include demographic information, NF1-related manifestations, documentation of data collection points, and actual data values including serum biomarkers and bone mineral density values. Investigative teams at each site have full access to data collected from participants enrolled through their site. There is limited access to date collected from other centers. Only the medical monitor, Dr. Spigarelli, and database manager, Mr. LaSalle, have full access to data collected from this study. Electronic Case Report Forms (CRFs) will be used for each participant. Participants must not be identified by name on any study documents that are sent off site to any agency. A Subject Identification Number (SIN) will be given by each site upon enrollment and then used to identify subjects on all associated paperwork, database, and/or regulatory documents could identify subjects.

Identifiers:
Human subjects will be identified at the time of enrollment from one of the 4 centers; UBC (University of British Columbia, Canada), UTA (University of Utah, USA), CIN (University of Cincinnati, USA), and HAM (University of Hamburg, Germany). The unique identifier will include the site followed by a 3-digit number starting with 100 ascribed sequentially at the time of enrollment at each site from:
UBC-100 to UBC-XXX
UTA-100 to UTA-XXX
CIN-100 to CIN-XXX
HAM-100 to HAM-XXX

This identifier will be used on all correspondence and only the investigative team at the enrollment site will be able to link the name with the identifier.

Disposition of Data
Electronic data from this study will be stored in the database embedded in the Informatics Core at the Center for Clinical Translational Science (CCTS) at the University of Utah.

Sharing Study Results
There are 3 instances where enrollees will receive information based on their enrollment in the study. The initial serum 25(OH)D will be conveyed to the enrollees as part of the screening test. Enrollees will know if they have sufficient vitamin D (no longer a participant in the trial), insufficient levels (randomized as an active participant in the trial), or severe deficiency that requires medical intervention. For participants in the trial, if the initial DXA scan identifies osteoporosis (bone mineral density that is -2 SD from the mean), the medical monitor will notify the coordinator who will notify the participant and their primary care provider to consider initiation of medical management, regardless of the serum 25(OH)vit D level. Third, the final results of each participant's BMD calculations, status of vitamin D3 dose randomization, serum calcium, serum iPTH, and serum 25(OH)vitD levels will be conveyed to the participant once available after the 2-year follow-up visit. They will receive an analysis and counseling regarding the results of their bone mineral density of spine and hip as determined by DXA scanning. These results will be shared with their primary care provider and may determine long-term care management for some participants.

Safety Monitor
Richard Kanner, M.D. will serve as the external safety monitor for this study. He will review recruitment and participant enrollment and monitor summarized data collection from the 4 sites as compiled by the Pediatric Clinical Trials Office. Dr. Kanner will review adverse events every 6 months and compile a report outlining his review of the medical monitor's data compilation. Dr. Kanner has authority to;

1) Stop the research protocol in progress;
2) Remove individual participants from the research protocol;
3) Initiate steps to protect the safety and well-being of participants until the University of Utah IRB and Human Research Protection Office (HRPO) of the U.S. Army Medical Research and Materiel Command can assess the safety monitor's report.

FDA ANNUAL REPORTS:
An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

PROTOCOL AMENDMENTS:
Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval. All amendments will be submitted to the FDA for review.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

Safety Monitoring and Interim Analysis
The medical monitor will review the entry serum 25(OH)vitD levels. He will notify the participating center of any serum vitamin D levels below 9 ng/mL, and these subjects will be taken off protocol and referred for evaluation and treatment of vitamin D deficiency.

Participants will be clinically monitored for signs and symptoms of hypercalcemia throughout the trial period. Interim analysis of the difference in change of BMD at the hip between subjects randomized to the 600 IU cholecalciferol and 4,000 IU cholecalciferol groups will be performed when 50 participants have completed the second DXA assessment. The trial will be stopped and all subjects offered therapy with 4,000 IU/day of cholecalciferol if the effectiveness of this treatment is clearly demonstrated ($p<0.01$) at either of these points.

RECORD KEEPING:
Per 21 CFR 312.57, investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified

STUDY ORGANIZATION AND POLICY

This is a randomized clinical trial of oral vitamin D therapy in adults with NF1 and vitamin D insufficiency, comparing the effects of a 600 IU daily supplement of cholecalciferol versus a therapeutic dose of cholecalciferol (4,000 IU/day) on maintenance of bone mineral density. This is an IND study, IND Number: 119135 and the IND holder is David Viskochil, MD, PhD, University of Utah PI. This study will be conducted in compliance with FDA, GCP Guidelines, regulatory and sponsor requirements, and protocol adherence. An audit may be conducted during the course of the study to ensure protocol adherence, regulatory oversight and appropriate subject reporting to Data Management and Analysis Center and the University of Utah.

The clinical centers are responsible for recruitment, following randomization procedures, study drug dispensing, all study-related medical and laboratory and imaging procedures and protocol mandated follow up procedures for a total of 80 study participants between the ages of 25 and 40 years.

Prior to screening procedures, all site personnel responsible for data entry must be familiar with study paperwork. Clinical report forms (CRF's) must be completed in a timely fashion with the lowest error rate attainable; addressing queries in a timely fashion, and completing required data forms. Clinical sites are responsible for maintaining current regulatory approvals for all study related activity through-out the study. Study related activities include: annual IRB renewals, training updates, laboratory accreditation and medical license renewals, and maintenance of local clinical site regulatory binders etc.

U of U and Data Management & Analysis Center
The trial is coordinated at the University of Utah (U of U). The U of U is responsible for the overall grant administrative function and is managed under Dr. David Viskochil's leadership in the Department of Pediatrics, University of Utah. Data Management at the U of U provides a place where all data collection and or information gathered from this trial will be stored for, analysis, and statistical support of this trial for the award period. Data management is under the leadership of Dr. Michael Spigarelli. The data manager (TBA) will work closely with the study team to ensure clinical sites are provided administrative, clinical and data guidance when needed.

The U of U is responsible for insuring regulatory compliance. The U of U will ensure that serious adverse events are reported to protocol chair and protocol team, medical monitor, sponsor and FDA according to the protocol in a timely manner. The U of U assists the protocol team in the implementation of the study. Dr. Spigarelli will assist in the data and quality control and will oversee the communications and governance of the study as it pertains to statistical and safety data reporting. The U of U is responsible for all regulatory reporting of the clinical sites to the DOD IRB, sponsor, data safety monitor, and medical monitor. Since this is an IND study using Ddrops, all safety reports will be initially reviewed by the data safety monitor and Dr. Viskochil. All safety reports will be sent to FDA by the U of U and all study sites are responsible for reporting safety reports to their regulatory agencies.

Department of Defense (DOD)
The U.S. Army (Department of Defense) is the funding agency for this NF1 Study. This trial is subject to the rules and regulations under the Army's leadership. The US Army Medical Research and Material Command regulate the trial. The University of Utah serves as a liaison for NF study and Dr. Viskochil will monitor and oversee regulatory mandates and compliance across all clinical sites, agencies and departments associated with this NF1 Study.

U of U Study Team
The study team will be the primary governing body of the NF1 multi-center trial and will be comprised of the Principal Investigators from the clinical centers noted as participating units on the previous page. The University of Utah and NF1 protocol team will provide at least monthly updates to study team of study's progress.

ESSENTIAL REGULATORY DOCUMENT EXPLANATION SHEET

All these documents should be kept in the Regulatory Files for each specific protocol after submission to the University of Utah's study coordinator, attention Carrie Bailey in PDF format if possible to carrie.bailey@hsc.utah.edu and the data manager. This will assist you in identifying and collecting all

the required regulatory documents you need to submit to the University of Utah **before** you can conduct the study.

Regulatory Requirements based on FDA requirements and GCP guideline Regulatory Binder Index

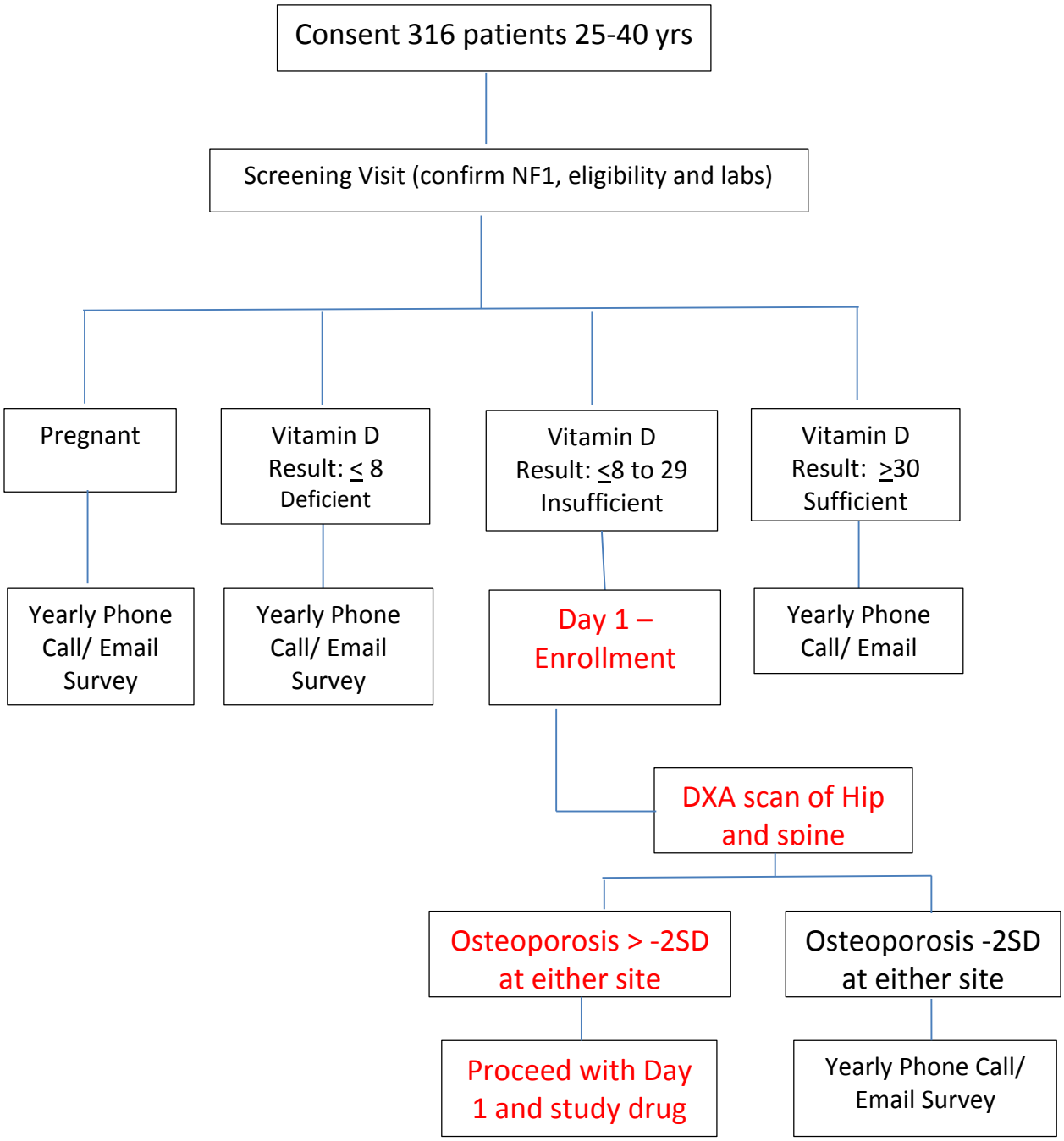
1. Protocol	**Study Protocol** **Study Protocol Amendments** **Protocol or Amendment Signature Pages** **Non-Disclosure Agreement** **Investigator Drug Brochure**
2. 1572 Regulatory Forms/CV	**Form FDA 1572 document *** **Curricula Vitae (signed & dated) *** **Medical Licenses (if applicable) *** **Financial Disclosure Agreement: kept in same folder, not in Regulatory File *** **Proof of research training***
3. Approved Consent Form(s)	**Informed Consent(s)***
4. IRB Approvals and Correspondence	**IRB/IEC/RAC Approvals for Protocol*** **Amendments, Advertisements, Renewals*** **IRB Correspondence (Progress reports, letters of submission for approval, IRB notification, responses to SAE reports, and IND Safety Reports, Etc.)****
5. Laboratory	**Lab Certifications (CAP & CLIA) *** **Laboratory Normal Ranges **** **CV pathologist, if applicable ****
6. Study Logs	**Personnel Delegation Log** **Monitor Site Visit Logs** **Site Signature Logs (may be on personnel delegation log** **Master Subject Logs** **Screening Logs** **Training Logs (Site initiation Visit attendance log & training certificates*)**
7. Correspondence	**Study related correspondence between the site, sponsor, regulatory agency, U of U, monitor, etc.**
8. Serious Adverse Events (SAE)	**Master SAE Reporting Form and Instructions** **Blank SAE Forms** **IND Safety Letters; DSMB reports** **Completed SAE Reports ** (or note where they are located)**
9. Drug Accountability	**Study Drug Receipt/packing invoices** **Study Drug Accountability Form** **Study Drug Supply Forms**
10. Miscellaneous	**Miscellaneous (CRF transmittal logs), etc.**

***send to U of U initially**

****send to U of U when available**

STUDY VISITS

Visit Schematic



Screening Visit:

- Consent
- Verify participant meets inclusion/exclusion criteria
- Blood draw:
    - The amount of blood required is about three teaspoons (15ml). 6ml Serum separator and 6ml plain red or serum separator (see lab section for processing instructions.
- The blood is to screen for serum 25(OH) vitamin D level. Other serum studies will be performed if the enrollee is found to be eligible for the remainder of the study. These tests include parathyroid hormone (a measure of bone metabolism) and calcium.
- 25 OH Vitamin D results:
    - Sufficient: $\geq$30ng/ml, These participants are not eligible and will be given their results and contacted yearly for a phone call or email survey.
    - Deficient: $\leq$8ng/ml – These participants are not eligible. They will be given their results and encourage to follow up with PCP for care and contacted yearly for a phone call or email survey.
    - Insufficient: 9ng/ml to 29ng/ml – These participants are eligible for enrollment.

Participants who are not treated (Sufficient or Deficient Vitamin D)
Yearly phone call/ email survey will be collected.

Participants who are eligible for enrollment – Insufficient will return for the following assessments
Day 1:

- Prior to visit send to Pediatrics Clinical Trials Office
    - Send inclusion/exclusion criteria
- DXA scanning will be performed of the spine and left hip –
    - If DXA results: Osteoporosis of -2SD at either site participant will be followed for yearly phone calls and is NOT eligible for study drug.
    - Participants should not be scanned if they have taken calcium in the last 24hrs or within 10 days of having any oral or IV radiologic contrast, and females should be asked to verify there is no chance of pregnancy and/or have a negative pregnancy test prior to the scan
- Pregnancy screening test. Those who are pregnant will have enrollment deferred to a later date.
- NF Physical Exam
- Questionnaires:
    - Quality of Life Questionnaire
    - Calcium Intake
    - Activity Questionnaire
    - Fracture history
- Randomization: Vitamin D_3 supplementation 600 IU or 4000 IU (see study drug)
- Tums or 400 mg elemental calcium per day.
- Diary: A diary is provided to keep daily track of missed vitamin D and calcium supplementation. Fractures, other adverse events, and concomitant medications should be noted on the diary.

6mo – Phone Call Visit and Study Drug Dispense

- Participants will be called to review AE and Concomitant medications review
- Dispense
- Vitamin D_3 supplementation 600 IU or 4000 IU (see study drug)

- Tums or 400 mg elemental calcium per day

12 mo – 1year (± 2weeks) – Clinic Visit

- Pregnancy test. Those who are pregnant will be discontinued from study drug.
- NF Physical Exam
- Questionnaires:
    - Quality of Life Questionnaire
    - Calcium Intake
    - Activity Questionnaire
    - Fracture history
- Blood draw:
    - The amount of blood required is about three teaspoons (15ml). 6ml Serum separator and 6ml plain red or serum separator (see lab section for processing instructions.
    - These tests include 25 OH vitamin D, parathyroid hormone (a measure of bone metabolism) and calcium.
- Dispense Vitamin D_3 supplementation 600 IU or 4000 IU (see study drug)
- Tums or 400 mg elemental calcium per day.
- Diary: Review and collect diary and dispense another year.
- Provided to keep daily track of missed vitamin D and calcium supplementation. Fractures, other adverse events, and concomitant medications should be noted on the diary.

18mo – Phone Call Visit and Study Drug Dispense

- Participants will be called to review AE and Con medications review
- Dispense
- Vitamin D_3 supplementation 600 IU or 4000 IU (see study drug)
- Tums or 400 mg elemental calcium per day

24 mo – 2 year (± 2weeks) – Clinic Visit

- Pregnacy test. Those who are pregnant will have discontinued from study drug.
- NF Physical Exam
- DXA scanning will be performed of the spine and left hip
    - Participants should not be scanned if they have taken calcium in the last 24hrs or within 10 days of having any oral or IV radiologic contrast, and females should be asked to verify there is no chance of pregnancy and/or have a negative pregnancy test prior to the scan
- Questionnaires:
    - Quality of Life Questionnaire
    - Calcium Intake
    - Activity Questionnaire
    - Fracture history
- Blood draw:
    - The amount of blood required is about three teaspoons (15ml). 6ml Serum separator and 6ml plain red or serum separator (see lab section for processing instructions.
    - These tests include 25 OH vitamin D, parathyroid hormone (a measure of bone metabolism) and calcium.
- Diary: Review and collect diary

STUDY DRUG

Cholecalciferol (Ddrops) are taken orally- 2 drop.
There is a dropper that automatically drops out a measured amount when the bottle is turned upside down. Each bottle lasts 3 months, and a new bottle with the same dose of cholecalciferol is provided after a diary is reviewed and an updated medical history provided to the study team. A total of 4 distributions will be made over the course of this 2-year study. The two doses of cholecalciferol were selected with respect to standard dosages in clinical care; 600IU per day (standard supplement), and 4,000IU (therapeutic dose). The prepared bottles have a metered dose of either 600IU or 4,000IU.

Participants are randomized to one or the other dose, and they take one measured drop orally, once a day. All randomization will be accomplished in site-specific blocks of 4 utilizing random number pre-assignments provided to each site, which will allow each site to utilize the correct blinded dose Vitamin D3. Block randomization by site (meaning equal distribution within a site is more important than equal random distribution across all sites) to account for variations in sun exposure and geographical location, while maintaining the highest protection for blinding in using a block size of 4.

Storage and Stability
Upon receipt of the study drug, bottles are to be stored at room temperature. Bottles should be protected from light. Bottles used for 1 subject may not be used for any other subject.

Availability
Distribution: Cholecalciferol will be distributed to site investigators directly from DDrops. Sites will be sent random labels for study drug labeling to blind study drug.

Preparation
There is a dropper that automatically drops out a measured amount when the bottle is turned upside down. Each bottle lasts 6 months, and a new bottle with the same dose of cholecalciferol is provided.

Ordering
Initial Shipments
When a site has received local IRB approval and Sponsor IRB approval the U of U Pharmacy will ship out the Cholecalciferol for distribution.

After Sponsor IRB approval the U of U will:
Place a call to U of U Pharmacy confirming the approval and then place the order for shipment.
Your site will be emailed the estimated day and time of arrival for the study drug.

Subsequent Shipments (active patients requiring additional Cholecalciferol supply)
If additional bottles of Cholecalciferol are required, the study site will need to complete an order form for a new shipment. Please give the U of U pharmacy 1 month notice for replacements.

For all drug shipments from U of U:
Cholecalciferol will be shipped with:

- A complete accountability record (including date of dispense, site name, quantity dispensed, and balance forward) will be recorded. Study accountability records are documented in CFR format and are kept in a secured area for duration of the study.
- Pharmacist review is required: a licensed pharmacist checks off package for accuracy of contents, authorizing order via 21 CFR compliant trial accountability log.

- Each shipment includes the following information:
- Study number
- IND caution statement and/or local regulatory statements
- Drug identification
- Lot number and expiration
- Storage conditions
- Dosing instructions (Take as directed per protocol)
- (Subject ID number, initials and date dispensed will be provided by study site pharmacy)
- Enclose a packing slip that includes the quantity of drug provided with a section to be completed once received by the site coordinator. This section includes confirmation of drug receipt, verification of package contents, and instruction to fax the completed packing slip to U of U.
- Process and ship authorized and completed orders will be processed and shipped the next business morning.

- All drug orders are shipped via *FedEx for Overnight* delivery.
- Packages are tracked until confirmed delivered and delivery. Packing slips with the shipment tracking number will be part of site study drug accountability records.

Once study drug is received at the clinical trial site:
The designated site coordinator validates that contents of package matches information provided on packing slip, signs off on the packing slip, and contacts U of U via email to validate shipment has been received and is accurate.

The order transaction is completed by entering the receipt confirmation and signed packing slip into the study file.

Sites will be required to send site drug accountability records to the U of U Pharmacy on a quarterly basis. The site study drug accountability records will be checked against U of U Pharmacy study drug administration data accountability records.

Randomization
Participants are randomized to one or the other dose, and they take two measured drop orally, once a day. All randomization will be accomplished in site-specific blocks of 4 utilizing random number pre-assignments provided to each site, which will allow each site to utilize the correct blinded dose Vitamin D3. Block randomization by site (meaning equal distribution within a site is more important than equal random distribution across all sites) to account for variations in sun exposure and geographical location, while maintaining the highest protection for blinding in using a block size of 4.

Randomization will be done by the University of Utah Pediatric Clinical Trials Office. Sites should send a request to the University of Utah Pediatric Clinical Trials Office, which will then electronically send a list of which bottles to dispense.

Drug Destruction
Sites will be instructed to destroy unused/returned drug per institution policy and note in the accountability record after site Pharmacy Drug Destruction Policy is sent to U of U and policy placed in site Regulatory Files.

U of U Investigational Pharmacist and contact information:
Investigational Pharmacy Service
University of Utah Hospitals & Clinics
Huntsman Cancer Hospital, 1950 Circle of Hope, Suite 2110, SLC, UT 84112
Pharmacy: (801) 585-0272 Fax: (801) 581-3744

Accountability
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the Cholecalciferol using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

Example:
Investigational Agent Accountability Record Template

Site # & Name:	Protocol No:
Study drug name:	Dose Form and Strength:
Protocol Title:	Dispensing Area:
Investigator Name:	

Line No.	Date	Patient's Initials	Patient's ID No.	Dose	Quantity Dispensed or Received	Balance Forward / Balance	Manufacturer and Lot No.	Recorder's Initials
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								
11.								
12.								

Supportive Care and Concomitant Therapy

There is no known interaction of Cholecalciferol with other concomitantly administered drugs. Prophylactic low-dose of calcium will be taken daily (400mg elemental calcium –oral).

LABORATORY PROCEDURES

Specimens to be Collected, Schedule of Collection, and Amount of Each Collection:
There are 3 laboratory studies to be performed at 3 collection points-including serum 25(OH) vitamin D, serum calcium, and serum iPTH at entry, 1 year, and 2 years. These values will be correlated with bone mineral density and dose of cholecalciferol as an analysis of the study. Serum will be processed from 15-ml blood draws at each of the 3 time-points. No other lab studies will be performed. These values are to help determine the effect of low- versus high-dose vitamin D3 on calcium metabolism and correlate to change in bone mineral density. If serum 25(OH) vitamin D is deficient at any time (entry, year 1, year 2) the participant will be notified.

Collection of specimen(s)

Sample Collection Time Points

Blood samples will be obtained at baseline, 12 months and 24 months.

Blood collection (needed for each time point sample)

- Collect about three teaspoons (15ml) of blood in 2 serum tubes. Glass tubes MUST NOT be used as they may break during transport and freeze-thaw cycles.
  - Heparin must not be used as an anticoagulant as it may interfere with testing

Vitamin D 25-Hydroxy-Serum sample collection:

- Collect: Serum separator tube.
- Unacceptable Conditions: EDTA plasma, grossly hemolyzed or lipemic specimens.
- Stability: After separation from cells: Ambient: 72 hours; Refrigerated: 1 week; frozen: 6 months

Parathyroid, intact with Calcium Serum sample collection:

- Collect: Serum Separator Tube.
- Unacceptable Conditions: Body Fluid (refer to Parathyroid Hormone, FNA, ARUP test code 2001491).
- Stability: After separation from cells: Ambient: 8 hours; Refrigerated: 48 hours; Frozen: 6 months

Handling of specimens

Vitamin D 25-Hydroxy-Serum sample collection:

- Specimen Preparation: Centrifuge for until there is a clear and definite separation between the cells and plasma/serum. Transfer serum to a Standard Transport Tube (STT).
- Storage/Transport Temperature: Freeze and then ship frozen on dry ice to UT for analysis.

Parathyroid, intact with Calcium Serum sample collection:

- Collect: Serum Separator Tube.
- Specimen Preparation: Allow serum specimen to clot fully at room temperature. Centrifuge for until there is a clear and definite separation between the cells and plasma/serum. Transfer serum to a Standard Transport Tube (STT). Transfer 2 mL or more serum or plasma to a STT.
- Storage/Transport Temperature: Frozen. Separate specimens must be submitted. Please aliquot 2 tubes; one for iPTH and one for calcium.

Prepare three labels each printed with Subject Study ID., Subject DOB, day/time of sample collection (24-hour clock format, i.e., 6:30 pm = 18:30). A label example is provided below and will be provided to all sites:

Subject Study ID:	Subject DOB:
Sample Type: Plasma	Investigator: :
Date of sampling: (mm/dd/yy)	Time of Sampling: (hh:mm) (24-hr format)
Comments:	

Clearly label tubes and store at -80°C.

When a sufficient number of samples have been collected, frozen plasma samples should be shipped to Carrie Bailey on DRY ICE in a Styrofoam box.

Shipping and analysis of specimen(s)

Ship all specimens to the following address:

Carrie Bailey CCRC
University of Utah
Division of Medical Genetics
50 North Mario Capechi Drive
Room 1C210 SOM
Salt Lake City- Utah 84132
Office-801-587-3605
Fax- 801-585-0269

All analyses will be performed within the ARUP Laboratories.

UA-HCG

Urine Pregnancy Test- All female subjects must have a negative urine pregnancy test to participate in the study. Those who are pregnant will have an opportunity to participate at a later date. Urine pregnancy tests will be performed at local sites.

DXA PROCEDURES

Image Acquisition

Each patient will be scanned on the same DXA system at their institution. Scanning will include the spine and left hip. Each scanning session must include the following sequences (although additional sequences can be performed per institutional protocol):

Participants should be scanned in light-weight clothing, preferably a hospital gown or a cotton t-shirt and scrub pants. Thick clothing, clothing with decals, glitter, rhinestones and metal (snaps, zippers, bra underwire, etc) should be avoided. The proximal femur should be positioned and analyzed according to manufacturer specifications; same with lumbar spine.

Participants should not be scanned if they have taken calcium in the last 24hrs or within 10 days of having any oral or IV radiologic contrast, and females should be asked to verify there is no chance of pregnancy and/or have a negative pregnancy test prior to the scan.

Scans should be done using patient ID number for name and date of birth only. The data for both sites, spine and left hip, will be transferred to a CD and shipped to Carrie Bailey at the U of Utah.

Day 1 DXA should be read at local site to confirm eligibility. Results of this study will not be divulged to either the participant or the investigative team unless the participant is osteoporotic according to the DXA study on site (T score less than -2SD). A CD will be accessed and data will be captured in the NF1 Vitamin D Study database. Only the data monitor will have access to the DXA data until the end of the study. DXA scanning is a standard procedure that is performed in a medical setting. Individuals are situated on a table for scanning and the procedure is completed in less than 30 minutes. The amount of radiation will be limited to about 6 mrem. For comparison, the annual background radiation exposure from the earth and atmosphere in an average person is roughly 300 mrem.

ADVERSE EVENTS **AND SERIOUS ADVERSE EVENTS**

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Each adverse event should be evaluated to determine:

1. SEVERITY OR GRADE USING CTCAE VERSION 4.0 (CTCAE) version 4.0 (http://ctep.info.nih.gov)
2. RELATIONSHIP OR ATTRIBUTION TO THE STUDY DRUG
    - Unrelated: bears no relation to timing of medication, similar to symptoms or signs expected in the disease process, does not recur on rechallenge.
    - Unlikely: does not have temporal relationship to intervention, could readily have been produced by the subject's clinical state, environmental, or other interventions, does not reappear or worsen with reintroduction of intervention.
    - Possibly: bears relation to timing of medication, similar to symptoms or signs expected in the disease process, does not recur on rechallenge.
    - Probably: bears clear relation to timing of medication, distinct from symptoms or signs expected in the disease process, does not recur on rechallenge.
    - Definitely: bears clear relation to timing of medication, distinct from symptoms or signs expected in the disease process, occurs on rechallenge.
3. Expectedness: if the adverse event is expected or unexpected. Expected adverse events related to administration of the study drug, can be found in Investigators' brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. Expected adverse events are also summarized in protocol.
4. Duration of the adverse event: start and end dates or, if continuing at final exam/assessment of subject.

5. Action taken: this may include whether no action was taken; study drug dosage was adjusted or temporarily interrupted; study drug was permanently discontinued; whether concomitant medication was taken; non-drug therapy given; hospitalization/prolonged hospitalization.
6. Whether the adverse event constituted a serious adverse event (SAE).

All observed or volunteered adverse events, regardless of suspected causal relationship to study drug, will be recorded as Adverse Events on electronic case report forms (eCRFs), and submitted to the Data Monitor within 2 weeks of its occurrence. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbation of pre-existing illnesses will be recorded. It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require that the subject be removed from treatment.

Unblinding:
Any safety issue deemed Unexpected and Related to Vitamin D3 would disallow continued participation in the protocol, and participant would be unblinded. Unblinding will be accomplished by having the site principal investigator contact the Director of the medical monitoring team who will provide the study arm assignment (low or high dose) for the withdrawn participant. For participants that have not been withdrawn from the protocol, determination regarding unblinding will be decided by PI from the respective site, the study PI, and the director of the medical monitoring team based upon the specifics of the request.

A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occurs, the subject will be given appropriate care under medical supervision until symptoms cease or until the condition becomes stable.

Adverse events are documented after the subject begins the study treatment and monitoring for AEs are a part of each follow-up visit. Timely and complete reporting of adverse events is a critical requirement in the conduct of this clinical trial. It allows the study to track the occurrence of events of a serious nature for review by the Data Safety Monitoring Board, sponsor (Department of Defense), regulatory agencies, institutional review boards and the investigators, in order to guard the safety of study participants.

Adverse event data will be collected and transferred to the U of U email reporting with 2 weeks. The U of U must be notified of $\geq$ Grade 4, unexpected adverse events that are at least possibly attributable to cholecalciferol or other research procedures will be reported within 24 hrs after investigator is made aware of the event. This should be reported within that time period to U of U by email and emailed to the data manager.

ADVERSE EVENT: TREATMENT
All adverse events should be treated appropriately. Such treatment may include interruption in study drug treatment which includes possible interruption (drug hold) or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution or until the patient meets off-study criteria as defined in protocol and assessed at all subsequent visits. (Patients with ongoing toxicity should be followed until the toxicity stabilizes or resolves.) Please note this drug has a few weeks half-life and the ***off study*** follow-up phone call is scheduled 12 weeks from last study treatment while the ***off treatment study visit*** is scheduled 30 days from last study treatment.

PREGNANCY

Any pregnancy that occurs during study participation should be reported.

To ensure patient safety those who are pregnant will have enrollment deferred to a later date. Those who are not pregnant will undergo randomization for high- versus low-dose vitamin D3 supplementation. DXA scanning will be performed of the spine and left hip as the primary endpoint of the clinical trial. Those who become pregnant will be removed from the supplementation and DXA scanning while remaining on the longitudinal studies until study end.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications. Site study coordinator will provide pregnancy notific
ation information and delivery documentation to the U of U data manger by email. The U of U data manger will send pregnancy information to the Study PI after receipt of information from study site coordinator.

Regulatory Notifications

Grade 1-3 unexpected and related adverse events will not be reported to the IRB in an expedited manner.

Only Grade 4 and higher unexpected adverse events, at least possibly attributable to cholecalciferol or other research procedures, will be reported to the regulatory officials and within 24 hours after the investigator is made aware of the event. The U of U will report Grade ≥ 4 unexpected and related AEs to local IRB and sponsor after receipt of information from study site coordinator. Study site will be responsible for notifying individual site regulatory agencies.

SERIOUS ADVERSE EVENTS/PROCEDURES

A Serious Adverse Event (SAE) is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening (Grade 4 or 5)
- Results in persistent or significant disability/incapacity
- Hospitalizations for Medical or Surgical Procedures: any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE. If subject is hospitalized to undergo a procedure as a result of an AE, report the AE responsible for the procedure (for example, report heart condition as AE instead of coronary bypass surgery).
- Is considered a significant medical event by the investigator based on medical judgment (may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes (life threatening, death, persistent or significant disability/incapacity).
- Pregnancy is reported as SAE if female subject becomes pregnancy while receiving therapy or within 30 days after last dose of study drug. Pregnancy outcome should be reported. Abortion, whether accidental, therapeutic or spontaneous is also reported as SAE. Any congenital anomaly/birth defect in a child born to a female subject exposed to cholecalciferol is also reported as separate SAE.

Inpatient hospitalizations for the following situations ***do not*** qualify as serious adverse events:

1. Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions
2. Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study;
3. Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

4. Treatment on an emergency outpatient basis for an event no fulfilling any of the definitions of a SAE given above and not resulting in hospital admission (e.g., ED visit without more than 23 hours hospitalization, or < 24 hours stay for transfusions)
5. Respite care

Any serious adverse event occurring after the patient has provided informed consent and after the patient has stopped study participation must be reported if attributed to prior cholecalciferol exposure.

Documents required for SAE reporting: MedWatch Form 3500A, SAE Report Form, de-identified documents, CRF entry
SAE Notification Time Table for Site

- **The U of U: 24 hours from Day of Awareness**
- **Sponsor notification: promptly (24 hours) from Day of Awareness; written report-within 3 days of Day of Awareness**

REPORTING SERIOUS ADVERSE EVENTS (SAEs)

Reporting Responsibilities

The Investigator or designee must notify the **U of U** as soon as possible by telephone or email of **all serious events** and Grade ≥4 related and unexpected adverse events. The University of Utah is responsible for notifying all required agencies of serious adverse events and ≥ Grade 4 unexpected, related AEs.

Any fatal (Grade 5) or unexpected life-threatening events (Grade 4) associated with the use of the drug or within 30 days of last study treatment/intervention must be reported to University of Utah within **24 hours** of Principal Investigator's initial receipt of information.

All adverse events are emailed by site study coordinator or CRA. Written documentation of Serious Adverse Events is provided on both the CRF and MedWatch Form as soon as information becomes available and completed within 24 hours of awareness. Relevant follow-up information should be submitted as soon as it becomes available.

All SAE documentation will be provided to University of Utah for transmission to Medical Monitor, Sponsor and Protocol Team. Relevant follow-up information should be submitted as soon as it becomes available.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse is detected, it should be followed until its resolution of until the patient meets off-study criteria and assessed at subsequent visits.

Summary: Site must notify the U of U and email data. After receipt of information from study site, the U if U is responsible for notifying the protocol team, IRB, the sponsor (Department of Defense), FDA and the Data and Safety Monitoring Board of all reported SAEs and significant AEs (≥ Grade 4 unexpected, related events). The site Principal Investigator is responsible for notifying their institutional regulatory agency according to site's institutional guidelines.

Medical records that include admission, laboratory report, progress notes and discharge summaries from the hospital should be requested. Any medical records obtained by the site in order to complete the SAE data forms should be filed in the participant's chart at the site. *Do not send copies of hospital records to U of U data manager unless specifically requested. Do send de-identified medical records to Operations Center for medical monitoring review. MedWatch Form also should contain only de-identified information and should be sent to the U of U.*

PROTOCOL DEVIATIONS:

Protocol deviations will be reported to the IRB as soon as possible after the PI learns of the deviation, but in all cases within 10 working days.